Childhood Pyogenic Meningitis: Clinical and Investigative Indicators of Etiology and Outcome

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The relevant parameters of 71 consecutive pediatric admissions for pyogenic meningitis at the University of Ilorin Teaching Hospital, Ilorin, Nigeria, were analyzed to identify possible clinical and nonmicrobiologic investigative clues of disease etiology and mortality. Cerebrospinal fluid (CSF) was Gram-smear positive (GSP) in 41 (57.6%) of the 71 cases. Twenty-three (56.1%) had Gram-positive cocci (GPC), 14 (34.2%) Gram-negative bacilli (GNB) and three (7.3%) Gram-negative diplococci (GND). The respective mean ages of GPC, GNB and GND cases were 4.49 ± 5.3, 3.06 ± 4.8 and 4.47 ± 4.9 years. *Streptococcus pneumoniae* accounted for 22 (78.6%) of the 28 CSF isolates (p=0.00), *Haemophilus influenzae* for two (7.1%) cases *and Neisseria meningitides* in one (3.5%). Anemia was significantly more common among GSP cases (p=0.04), as was convulsion among those with GNB-positive smears (p=0.03) and a bulging fontanelle in the Gram-smear-negative category. Otherwise, the prevalence and resolution times of the other clinical parameters were comparable across the etiological categories. There were 30 deaths (42.3%) among which GNB-positive cases had significantly shorter stay (p=0.045). Mortality was significantly higher in those with an abnormal respiratory rhythm at admission (p=0.04), purulent/turbid CSF (p=0.03), CSF protein of >150 mg/dl (p=0.02) and glucose <1 mg/dl (p=0.047).

Our findings highlight the inherent limitations of predicting the etiology of pediatric meningitides from the clinical parameters as well as the poor prognostic import of respiratory dysrhythmia and a profoundly deranged CSF protein and glucose. The etiological burden of GPC/*S. pneumoniae* in childhood meningitides in sub-Saharan Africa, the propensity of GNB/*H. influenzae* for quick fatality and the need for the relevant preventive vaccines are expounded in the discussion.

Key words: meningitis ■ infection ■ Nigeria ■ West Africa ■ developing countries ■ children/adolescents

© 2007. From the Department of Pediatrics & Child Health, University of Ilorin Teaching Hospital (Johnson, Adedoyin, Abdul-Karim); and Olanrewaju Hospital (Olanrewaju), Ilorin, Nigeria. Send correspondence and reprint requests for *J Natl Med Assoc*. 2007;99:937–947 to: Dr. Abdul-Wahab B. Rotimi Johnson, Professor of Pediatrics, Department of Pediatrics & Child Health, University of Ilorin, PMB 1515, Ilorin, Nigeria; phone: +234 31 8033946052; fax: +234 31 2220020; e-mail: wahabjohnson@yahoo.com

INTRODUCTION

Pyogenic meningitis remains a significant cause of preventable childhood deaths and indeed a major cause of (long-term) neurological deficits and physical handicaps in children.[1-5] Whereas specific treatment is eventually determined by the definitive microbiological characteristics of the cerebrospinal fluid (CSF) isolates, the clinical import of a belated (appropriate) treatment continues to justify a prompt initiation of efficacious empirical antimicrobials while awaiting specific laboratory data.[7-9] In sub-Saharan Africa and perhaps many other countries in the developing world, the paucity of appropriate laboratory facilities and skilled personnel in most first- and second-level health facilities has often compelled clinicians to complete the entire course of empirical treatment without recourse to the relevant microbiological guide. It follows, therefore, that for a meaningful reduction in the current high mortality profile of pediatric pyogenic meningitis in third-world countries, there is a clear need for exploring the clinical parameters of possible disease etiology and, hence, the initial choice of antimicrobial therapy. The identification of these clinical parameters, as well as some nonspecific investigative correlates of disease etiology and fatality, constitutes an invaluable "low-tech" tool for evolving the relevant empirical therapeutic recommendations. This is particularly so for the frontline clinician with little or no access to microbiological facilities. With these in mind, the present study was undertaken partly to determine the possible clinical and nonmicrobiologic investigative clues of disease etiology, as well as identifying those presenting parameters that portend a poor short-term disease outcome. It was also our hope that the findings of the present study would subsequently provide the scientific bases for updating the current local therapeutic policies on pediatric meningitis.

PATIENTS AND METHODS

Background Data on the Study Population and Hospital

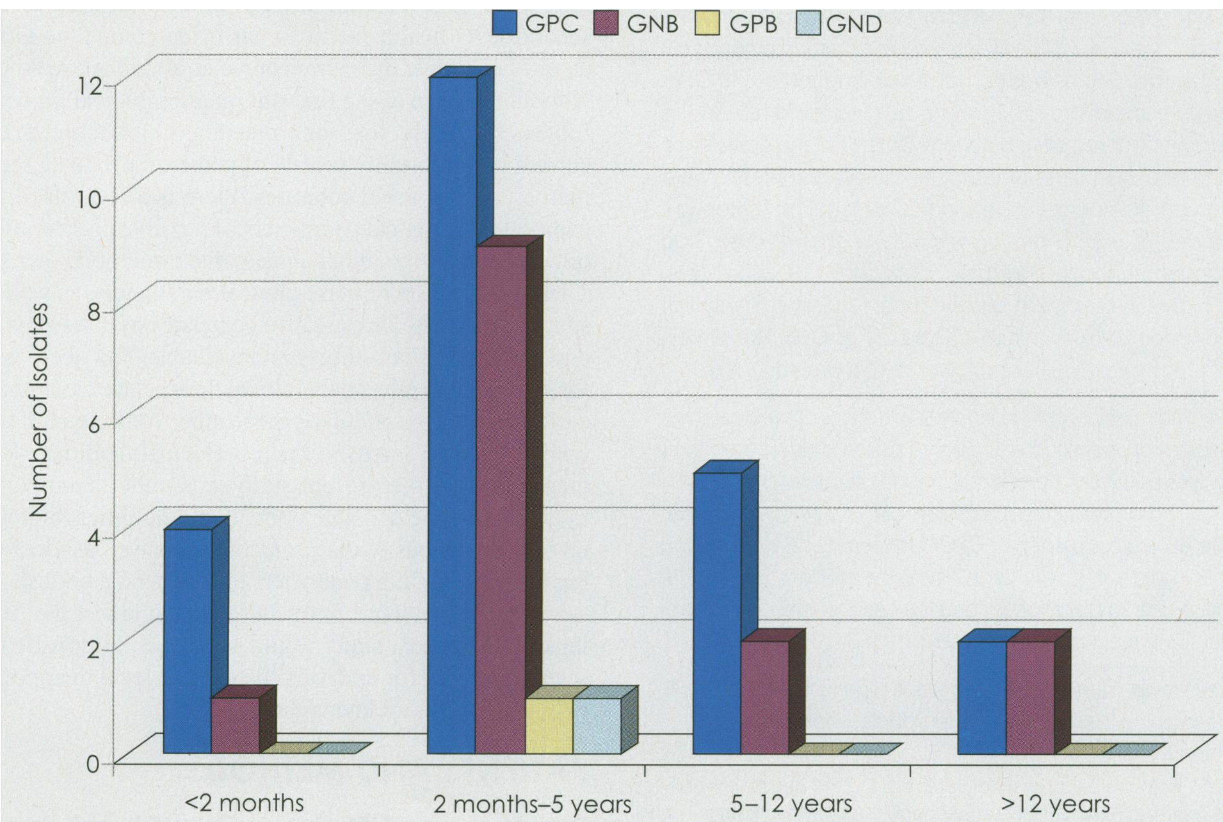
The present communication emanated from a five-year review of the clinical and microbiological data of consecutive emergency pediatric unit (EPU) admissions for pyogenic meningitis at the University of Ilorin Teaching Hospital (UITH), Nigeria. The EPU has 20 beds and provides in-patient transitional care for children aged <16 years. The majority of patients are from Ilorin, a city located in the Guinea-Savannah zone, which lies within the sub-Saharan meningococcal belt.[10] The EPU also receives referrals from the adjoining north-central and southwestern states of Nigeria.

Methodology

Potential cases were first identified from the admission register, after which the clinical laboratory data were obtained from their individual case records. For potential cases with the relevant clinical parameters (e.g., fever, convulsion, irritability, impaired consciousness, bulging fontanelle, etc.), diagnostic confirmation was predicated on the CSF findings of ≥1 of a positive Gram stain and/or culture for bacterial agent(s), pleocytosis of >5 leukocytes with polymorphonuclear predominance, an elevated CSF protein (>40 mg/dL) associated with hypoglycorrhachia (<40 mg/dL) and/or CSF glucose <50% of the concomitant serum value.[9,11] Those with a discharge or postmortem diagnosis of pyogenic/bacterial meningitis had appropriate verification of the microbiologic data from duplicate laboratory records, and cases without verifiable microbiological data were excluded from further analyses. The following data were obtained from the records of eligible cases:

1. The Gram smear, cellular profile, bacterial isolates and sensitivity data (from cultures) of the initial CSF obtained, as well as the relevant (CSF) biochemical parameters such as protein, glucose and, in some cases, the concomitant random blood sugar;
2. Relevant clinical parameters, including date/month of admission, demographic data, identifiable short-term complications (including neurological deficits), and the preadmission duration and resolution times of some presenting symptoms/signs;
3. Hematological indices, including the hemoglobin genotype results as available in the case records of those with the relevant clinical parameters;
4. The serum electrolytes results as available;
5. Outcome variables comprising one of "death," "survival" or "discharge against medical advice."

Figure 1. Gram-smear results according to age groups



Gram-smear categories of cases of pyogenic meningitis according to age groups. The Gram-smear distribution was not significantly different between the age groups ($P=0.63$; $\chi^2=0.91$); GPC: Gram-positive cocci; GNB: Gram-negative bacilli; GPB: Gram-positive bacilli (eventually yielded aerobic spore bearers on culture); GND: Gram-negative diplococci

Other outcome variables extracted were the duration of hospital stay for survivors and fatal cases.

Treatment

Empirical antimicrobials comprised one of either penicillin G (crystalline penicillin)–chloramphenicol combination, or ampicillin and chloramphenicol; appropriate monotherapy was substituted on receiving the relevant microbiologic data. A few cases had one of ceftriaxone, cefuroxime, ceftazidime or sultamicillin (Unasyn®), either because of poor response to empirical therapy and/or lack of CSF sterilization after 48–72 hours, or on account of a long prehospitalization symptom duration. Standard supportive treatment[9,11,12] was offered as available.

Data Analyses

The clinical and microbiologic data were analyzed using the EPI-INFO statistical package of a microcomputer. The Chi square (with or without Yates' or the Mantel-Haenzel correction) or the Fisher's exact tests (FET) were used as appropriate. The confidence intervals (CIs), odds ratio (OR) and relative risk (RR) were obtained as applicable. Analysis of variance (ANOVA) test was used for comparing mean values. Significant association was presumed if $p<0.05$.

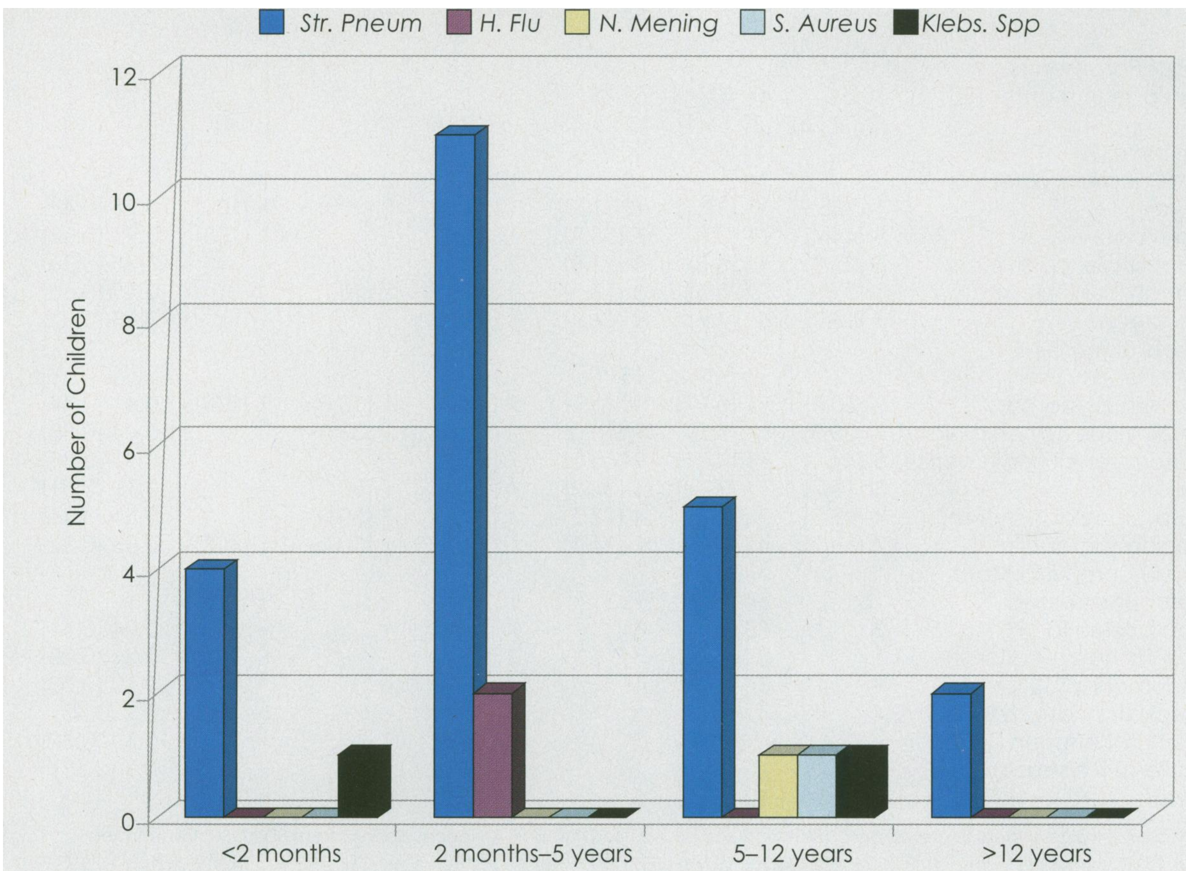
RESULTS

Over the five-year period, an admission diagnosis of pyogenic meningitis was sustained on discharge or at postmortem in 71 cases, including the two with tuberculous meningitis (TBM). The total number of EPU admissions over the same period was 9,603. Hence, pyogenic meningitis constituted 0.74% of all EPU admissions over the study period. A peak admission rate was recorded between August/September and February of successive years, with a transient rise in April. This peak coincided with the dry but cool and dusty harmattan and the hot, dry seasons. The lowest trough in monthly admission rates was recorded with the advent of the rains in May.

Demographic Parameters and CSF Variables

The 71 cases comprised 43 males and 28 females; the male:female ratio was 1.5:1. Fifty-one (72%) cas-

Figure 2. CSF bacterial isolates according to age groups



Cerebrospinal fluid bacterial isolates in infants and children according to age groups. Note the preponderance of *Streptococcus pneumoniae* isolates in all age groups, including young infants, aged <2 months; Isolates were not significantly different between the age categories ($p= 0.4$; $\chi^2=1.85$). Str. Pneum.: *Streptococcus pneumoniae*; H. Flu: *Haemophilus influenzae*; N. Mening.: *Neisseria meningitidis*; S. aureus: *Staphylococcus aureus*; *Klebsiella Spp.*: Klebsiella species es were aged ≤5 year. Twelve (17%) were ≤2 month. A significantly higher male preponderance was seen in the 2 month–5-year-olds (p=0.04; RR=1.6; OR=1.60; 95% CI: 0.88–11.09).

Of the 28 cases for whom documented macroscopic characteristics of the CSF were confirmed in the laboratory register, 18 (64.2%) had a turbid CSF, while the appearances in six (21%) and three (10.7%) others were recorded as purulent and xanthochromic respectively. A positive Gram-smear (GSP) was obtained in 41 (57.7%) of the 71 cases, while 30 (42.3%) others with corroborative clinical and/or CSF biochemical parameters of pyogenic meningitis had Gram-smear negative (GSN) CSF; two of the latter had clinical and/or CSF features of TBM. The Gram-smear categories of the 41 GSP cases according to the age groups are shown in Figure 1. Twenty-three (56.1%) smears had Gram-positive cocci (GPC); Gram-negative bacilli (GNB) accounted for 14 (34.2%) cases, while only three (7.3%) had Gram-negative diplococci (GND). The mean age for GPC cases was 4.49 years (SD=5.3, n=23). For those with GNB- and GND-positive smears, the mean ages were 3.15 years (SD=4.8, n=14) and 4.47 years (SD=4.9, n=3), respectively.

As shown in Figure 2, *Streptococcus pneumoniae* was isolated in 22 (78.6%) of the 28 culture-positive CSF analyses, and this proportion was significantly higher than the corresponding one for *Haemophilus influenzae* [two (7.1%) cases]; *Neisseria meningitidis* was identified in one (3.6%) case (p=0.00). Other isolates were Klebsiella species in two (7.1%) cases, *Staphylococcus aureus* and aerobic spore bearers in one (3.6%) case each. The latter was a case with Gram-positive bacilli

Table 1. Clinical parameters according to CSF Gram-smear categories in 71 cases of pyogenic meningitis

	Partially Treated	Total	Gram-Smear Categories				P Values
	GSN	GSP	GPC	GNB	GNC	GPB	GSN vs. GSP (GPC vs. GNB/ vs. GNC)
# of Cases	30	41	23	14	3	1	~
Freq. (%)	42.3	57.7	56.1	34.2	7.3	2.4	~
Clinical Parameters							
Mean age in months (SD; n)	30.61 (35.8;25)	47.40 (59.6;41)	53.89 (63.5;23)	36.71 (57.5;14)	53.67 (59.5;3)	12 (~; 1)	0.24* (0.70)
Symptoms (%)							
Total number assessed	18	34	18	13	2	1	
Fever	16 (88.9)	33 (97.1)	18 (100)	12 (92.3)	2 (100)	1 (100)	0.27 (0.42)
Convulsion	8 (44.4)	17 (50)	7 (38.9)	11 (84.6)	-	1 (100)	0.93 (0.03)§
Irritability/excessive cry	5 (27.8)	9 (26.5)	5 (27.8)	2 (15.4)	1 (50)	-	0.27 (0.36)
Cough/breathlessness	1 (5.5)	7 (20.6)	3 (16.7)	2 (15.4)	2 (100)	-	0.15 (0.66)
Headache	3 (16.7)	6 (17.7)	3 (16.7)	3 (23.1)	-	-	0.63 (0.50)
Physical Signs (%)							
Number assessed	18	34	18	13	2	1	-
Drowsiness/coma	9 (50.0)	21 (64.7)	10 (55.6)	9 (69.2)	1 (50.0)	1 (100)	0.41 (0.44)
Neck stiffness/menin. signs	7 (38.9)	17 (50)	9 (50.0)	7 (53.8)	1 (50.0)	-	0.64 (0.88)
Motor/cranial nerve deficits	8 (44.4)	16 (47.1)	9 (50.0)	7 (53.8)	-	-	0.91 (0.88)
Pallor	3 (16.7)	11 (32.4)	6 (33.3)	4 (30.8)	1 (50.0)	-	0.19 (0.51)
Resp. signs/abn. rythm.	4 (22.2)	9 (26.5)	4 (22.2)	4 (30.8)	1 (50.0)	-	0.51 (0.45)
Bulging fontanelle	7 (38.9)	4 (11.8)	2 (11.1)	1 (7.6)	1 (50.0)	1 (100)	0.03 (0.62)§
Compl./Comorbid State							
Number assessed	18	34	18	13	2	1	
Signif. anemia (PCV <25%)	2	13	8	4	1	~	0.04 (0.44)§
Cranial nerve deficit(s)	1	5	3	2	~	~	0.31 (0.38)
Pneumonia	~	5	1	4	~	~	0.12 (0.08)
Respiratory dysrhythmia¶	4	4	3	1	~	~	0.9 (0.43)
Subdural effusion	~	4	2	1	1	~	0.17 (0.62)
Sickle cell disease	1	1	1	~	~	~	0.9 (0.58)
Others¶¶	3	12	5	8	~	~	~

§ Significant p value(s) identified as shown; * Statistical testing was ANOVA, with variances derived from SD²; GSN: Gram-smear negative; GSP: Gram-smear positive; GPC: Gram-positive cocci; GNB: Gram-negative bacilli; GNC: Gram-negative cocci; GPB: Gram-positive bacilli; respiratory dysrhythmia: abnormal respiratory rhythm, comprising ≥1 of Cheyne-Stokes' respiration, Biot's breathing or intermittent apnea. ¶¶: Comprise three with persistent gait abnormality and/or motor deficits, five cases with pneumonia, two cases each with subdural effusion, suppurative otitis media, septic arthritis and pathologic jaundice, and one each with hydrocephalus, cortical blindness, deafness, aphasia, persistent focal seizure, syndrome of inappropriate SIADH secretion, Klebsiella septicemia, meningococcemia and metabolic acidosis

(GPB) smear, which was later disregarded as a contaminant. The frequencies of isolates were similar amongst the age groups ($p=0.40$; $\chi^2=1.85$).

Clinical Parameters According to Etiological Categories

As shown in Table 1, a significantly higher proportion of cases in the GNB category, compared with GPC cases, had convulsed before presentation ($p=0.03$; OR=0.12; 95% CI: 0.01–0.83). On the other hand, anemia (packed cell volume of <25%) was more frequently seen in the GSP category, compared with GSN cases ($p=0.04$; OR=0.20; 95% CI: 0.02–1.12), while a bulging anterior fontanelle was commoner amongst GSN cases ($p=0.03$; OR=4.77; 95% CI: 0.95–26.01). The prevalence of altered consciousness (drowsiness or coma), which was noticeably higher in GNB cases, did not reach a significant level ($p=0.44$; $\chi^2=0.59$). Also, the prevalence of neurological deficits at admission was comparable between GSP [16 (47.1%) out of 34] and GSN [eight (44.4%) of the 18] ($p=0.91$) cases, and between GPC and GNB ($p=0.88$). The cases with neurological deficits included six with cranial nerve palsies (including four with facial (VII) nerve palsy. One of four had a concomitant VIII nerve palsy, while two others had perceptive deafness (VIII nerve palsy) and cortical blindness, respectively.

The comorbidities in relation to the smear categories included severe anemia (requiring blood transfusion) in six (46.2%) of the 13 GSP cases. Two cases (both of whom died) had a laboratory confirmation of sickle cell disease. One of these was GPC positive, and *S. pneumoniae* was cultured from the CSF of the same child. Although the frequencies of the other clinical parameters (including complications) did not differ significantly across the Gram-smear categories, six deaths were recorded amongst the eight cases whose respiration was irregular at admission (vide infra).

A comparison of the prevalence of the clinical parameters among the three major bacterial (etiological) categories is shown in Table 2. Although the prevalence of each of convulsion, altered consciousness and neurological deficits was higher amongst *H. influenzae* cases, a meaningful statistical comparison of the clinical parameters was difficult to ascertain in view of the small sample sizes of the *H. influenzae* and *N. meningitidis* isolates. The mean preadmission symptom duration and the postadmission resolution times of selected clinical parameters are compared between the Gram-smear categories in Table 3. The preadmission duration of convulsion was apparently longer amongst GPC cases, whilst the mean postadmission resolution times of seizures and coma were about 1.4 and 1.3 times longer in GNB cas-

Table 2. Clinical parameters according to CSF isolates in children with bacterial meningitis

	Total # of Isolates	Bacterial Isolates					P Value
		S. pneum.	*S. aureus*	*H. influ.*	*Klebs. spp.*	*N. menig.*	(*S. pneum.* vs *H. influ.*)
Total Number Assessed	28	22	1	2	1	1	0.00§
Freq. (%)	70.7	78.6	3.5	7.1	3.5	3.5	
Clinical Parameters							
Symptoms (%)							
No. assessed	22	17	1	2	1	1	
Fever	22 (100)	17 (100)	1 (100)	2 (100)	1 (100)	1(100)	~
Convulsion	12 (54.6)	7 (71.2)	-	2 (100)	1 (100)	-	0.21
Irritability/exc. cry	5 (22.7)	5 (29.4)	-	-	-	-	~
Cough/breathlessness	3 (13.6)	3 (17.6)	-	-	-	-	~
Headache	4 (18.2)	2 (11.8)	-	-	1	-	~
Physical Signs (%)							
No. assessed	22	17	1	2	1	1	
Coma/impaired Consciousness.	13 (59.1)	10 (58.8)	-	2 (100)	1 (100)	-	0.39
Neck stiffness/ meningeal signs	9 (40.9)	7 (41.2)	-	1 (50)	1 (100)	-	~
Motor/cranial Nerve deficits	9 (40.9)	6 (35.3)	1 (100)	2 (100)	-	-	0.16
Pallor	7 (31.8)	6 (35.3)	-	1 (50)	-	-	~
Resp. dysrhythmia	5 (22.7)	4 (23.5)	-	1 (50)	-	-	~
Bulging fontanelle	2 (9.1)	2 (11.8)	-	-	-	-	~

§ *S. pneumoniae* constituted a significantly higher proportion of the total isolates; p value derived from *S. pneumoniae* vs. *H. influenzae* vs. others was 0.10; $\chi^2=4.59$; df=2; ¶: Fishers' exact test (FET), Yates' or Mantel-Haenszel corrected Chi-squared test used for rows with >1 *H. Influenzae* isolates.

es compared with those with GPC. However, a statistical comparison of these mean values using the ANOVA test showed no significant differences among the Gram-smear categories (Table 3).

Laboratory Parameters according to Etiological Categories

As shown in Table 3, the mean values of the CSF protein and sugar, hematocrit and serum sodium were comparable across the Gram-smear categories. Incomplete records of some of the relevant investigative data (with the corresponding small sample sizes), however, precluded a meaningful statistical analysis of some of the relevant investigative data.

Table 3. Mean preconsultation duration and resolution times of selected symptoms and investigative parameters according to cerebrospinal fluid

	Gram-Smear Categories					P Value
	Partially Treated/GSN Mean ± SD (Variance; n)	GPC Mean ± SD (Variance; n)	GNB Mean ± SD (Variance; n)	GNC# Mean ± SD (Variance; n)	GSP Mean ± SD (Variance; n)	GSN vs. GSP (GPC vs. GNB vs. GNC)
Symptom Duration #						
Fever	5.0 ± 3.41	4.12 ± 3.14	3.55 ± 2.30	4.75 ± 0.35	4.08 ± 2.36	0.35 [0.63]
	(11.61; 14)	(9.60; 16)	(5.29; 11)	(0.13; 2)	(5.57; 29)	
Convulsion	1.63 ± 0.92	2.71 ± 1.25	1.78 ± 0.97	~	2.19 ± 1.16	0.24 [0.11]
	(0.84; 8)	(1.57; 7)	(0.95; 9)	~	(1.36; 16)	
Irritability/excessive cry	3.4 ± 2.88	2.75 ± 0.5	4.5 ± 2.12	4.5 ± 0.71	3.6 ± 1.3	0.67 [0.12]
	(8.29; 5)	(0.25; 4)	(4.50; 2)	(0.50; 2)	(1.70; 8)	
Cough/breathlessness	8.5 ± 2.12	3.0 ± 2	4.5 ± 2.12	4.75 ± 0.35	3.93 ± 1.69	0.22 [0.51]
	(4.5; 2)	(4.0; 3)	(4.50; 2)	(0.13; 2)	(2.87; 7)	
Headache	23.33 ± 31.82	9 ± 12.73	0.9 ± 0.14	~	6.30 ± 10.71	0.44 [0.34]
	(1012.32; 3)	(162.05; 4)	(0.02; 42	~	(114 .7; 6)	
Mean Symptom Resolution Times (Days)‡#						
Fever Clearance Time	3.2 ± 1.62	4.17 ± 1.17	2.83 ± 1.72	~	4.08 ± 1.38	0.18 [0.14]
	(2.62; 10)	(1.37; 6)	(2.97; 6)		(1.91; 13)	
Seizure Resolution Time	2.57 ± 1.13	2.5 ± 0.58	3.40 ± 2.07	~	2.9 ± 1.52	
	(1.29;7)	(0.33; 4)	(4.3; 5)		(2.32; 10)	0.63 [0.42]
Coma Resolution Time	5.67 ± 4.04	6.33 ± 3.22	8.50 ± 5.57	~	7.57 ± 4.50	0.54 [0.56]
	(16.33; 3)	(10.33; 3)	(31.0; 4)		(20.3; 7)	
CSF Biochemistry#						
Mean CSF protein	195.4 ± 167.79	280.1 ± 300.36	188 ± 50.99	176.5 ± 109.6	247.30 ± 246.4	0.55 [0.69]
		(28154.93; 10)	(90218.98;15)	(2600; 6)	(12012.5; 2)	(60713.8; 23)
Mean CSF glucose	2.15 ± 1.24	1.28 ± 1.34	2.23 ± 1.23	~	1.763 ± 1.44	0.51 [0.13]
	(1.54; 8)	(1.79; 12)	(1.50; 7)		(2.08; 20)	
Hematological Parameters¶#						
Packed cell volume	31.88 ± 6.36	24.7 ± 5.85	30.6 ± 6.91	~	26.4 ± 6.91	0.07 [0.10]
	(40.41; 8)	(34.23; 10)	(47.8; 5)		(47.69; 15)	
Total WBC $\times 10^9$/L	7.75 ± 4.08	10.55 ± 4.58	11.3 ± 6.79	~	11.3 ± 5.3	0.15 [0.8]
	(16.64; 6)	(21.00; 11)	(46.15; 4)	(28,13 : 16)		
% Polymorphs	75.5 ± 16.26	66.50 ± 12.29	~	~	73 ± 17.22	0.86 [~]
	(264.5; 2)	(151; 4)			(296 .5; 5)	
Others#:						
Serum sodium	~	129.3 ± 8.33	130 ± 4.62	~	130 ± 4.62	[0.88]
	(69.33; 3)	(21.33; 4)			(21.33; 4)	

i) ¶: Only mean percentages are compared; Statistical method was ANOVA; i) ‡: Mean, SD and variance not applicable because of inadequate sample size. The only survivor of the three GNC cases had fever clearance and seizure resolution times of five and two days, respectively; ii) # Empty cells in some rows occasioned by inadequate sample size/incomplete documentation in the corresponding Gram Smear categories, thus precluding a valid statistical comparison; iii) Two of the three cases died before full clinical and investigative assessment; GNC and *N. meningitidis* identified after death. The fever clearance and seizure resolution times in the remaining one case were five and two days, respectively; iv) The duration of the selected symptoms and the resolution times of fever, convulsion and coma did not differ significantly between the smear categories; v) For fever duration in *S. pneumoniae* vs. *H. influenzae* cases, the respective p value and F statistics were 0.79 and 0.07 using ANOVA; For convulsion, the respective values comparing the two Gram-smear categories were 0.50 and 0.48. A similar comparison of the other selected symptoms was precluded by the inadequate sample sizes in the relevant Gram-smear categories categories; vi) GPC: Gram-positive cocci; GNB: Gram-negative bacilli; GNC: Gram-negative cocci; GSN: Gram-smear negative, including tuberculous meningitis; GSP: Gram-smear positive (i.e., GPC+GNB+ GNC)

Admission Outcome in Relation to Demographic, Clinical and CSF Microbiologic Parameters

As shown in Table 4A, a total of 30 (42.3%) deaths were recorded, including one of the two with TBM. Although children aged 2 months–5 years constituted 20 (58.9%) of 34 cases, age was not significantly associated with mortality (p=0.19). Similarly, with 18 (41.8%) vs. 12 (42.9%) deaths in males and females, respectively, fatality was not significantly influenced by gender (p=0.65). Irregular respiration at or soon after admission was, however, associated with a significantly higher mortality. Excluding the one case who had been discharged against medical advice, six (85.7%) of the remaining seven with any of intermittent apnea, Cheyne-Stoke's, Biot's or periodic respiration eventually proved fatal (p=0.04, FET). On the other hand, presumably late signs/complications, such as a bulging fontanelle, coma, subdural effusion and a positive Kernig's, sign did not portend a fatal disease outcome (Table 4A).

With regard to investigative parameters, a significantly higher mortality was seen in those with a purulent/turbid CSF (Table 4B). Fifteen (65.5%) of the 24 with a turbid or purulent CSF died, as against one (5.9%) of seven cases with a clear or xanthochromic fluid (p=0.03, OR=0.10; 95% CI: 0.00–1.10). Similarly, an initial CSF protein >150 mg/dl, and CSF glucose <1 mg/dl correlated significantly with mortality. Neither the CSF-smear category nor the ultimate bacterial isolates were associated with a fatal disease outcome (Table 4B). Whereas no death was recorded in the two GNB cases whose CSF grew *H. influenzae*, the only GNC case (a 10-year-old) with *N. meningitidis* isolate proved fatal.

Table 5 shows the smear-specific duration of hospital stay in survivors and fatal cases. Whilst the mean duration of admission in survivors was comparable between the smear categories, fatal cases in the GNB category had a significantly shorter stay before demise, compared with the GPD group (p=0.04, FET).

Table 4A. Outcome indicators 1: admission outcome according to selected demographic, clinical and CSF macroscopy variables

Parameters	Admission Outcome						P Value
	Survived	Died	DAMA¶	Total	Total Assessed	% Mortality	
Demographic Parameters:						-	
Age							
<2 months	8	4	~	12	12	33.3	
2 months–5 years	14	20	5	39	34	58.9	
5–12 years	9	3	4	16	12	25.0	0.19
>12 years	1	3	~	4	4	75.0	
Gender							
Male	21	18	4	43	39	41.8	
Female	11	12	5	28	23	42.9	0.65
Clinical Parameters/ Associated Conditions	n=32	n=30	N=9	n=71	n=62	~	
Coma	8	7	3	18	15	46.7	0.89
Motor Deficits	7	6	1	14	13	46.1	0.9
Signif. Anemia (PCV <25%)	7	4	2	13	11	36.4	0.58
Positive Kernig's Sign	6	2	3	11	8	25.0	0.15
Cranial Nerve Deficit(s)	3	1	1	5	4	25.0	0.33
Pneumonia	2	1	2	5	3	33.3	0.52
Respiratory Dyshrythmia	1	6	1	8	7	85.7	0.04§
Bulging Fontanelle	3	1	~	4	4	25.0	0.65
Subdural Effusion	1	1	~	2	2	50.0	0.74
Sickle Cell Disease	~	2	~	2	2	100.0	0.23
Cerebrospinal Fluid Appearance (n=31)#							
Turbid	8	10	3	21	18	55.6	
Purulent	1	5	~	6	6	83.3	
Xanthochromic/Blood Stained	2	1	~	3	3	33.3	0.03§
Clear and Colorless	4	~	~	4	4	0	
Unknown¶¶	15	13	9	37	~	45.2	

#: For the purpose of statistical analysis, values in the "turbid " and "purulent" cells are pooled together, while those in the "xanthochromic/blood-stained" cells are pooled with those of the "clear and colorless"; ¶: Refers to discharge against medical advice and hence had incomplete data record; ¶¶: Attributable to incomplete documentation of CSF parameters; excluded from statistical testing

Sensitivity Patterns of CSF Bacterial Isolates

Of the limited spectrum of antimicrobial sensitivities explored, 12 (92.3%) of the 13 isolates of *S. pneumoniae* were sensitive to crystalline penicillin (penicillin G). A comparable proportion (93.3%) of the same pathogen was sensitive to ampicillin. The drug-resistant isolates were recorded towards the end of the five-year review. All the pneumococcal and *H. influenzae* isolates tested (100% each) were, however, sensitive to each of ceftriaxone, cefuroxime, ceftazidime and sultamicillin (sulbactam-ampicillin combination (Unasyn). The two *H. influenzae* isolates were also sensitive to ampicillin; one of the latter was resistant to chloramphenicol.

DISCUSSION

The hot, dry, seasonal and harmattan surge in hospital admission was consistent with earlier observations,[4,8,17,21] while the preponderance of under-fives underscores the age group that bears the brunt of the disease burden. Possible public health interventional import of these observations includes the possible timing of preventive campaigns to coincide with the seasonal trough and the identification of the preschool age as the target population for future local/regional vaccine prevention of invasive lesions associated with the predominant pathogens.

The comparable prevalence of most of the common symptoms and signs of meningitis across the major etiological categories in the current study reflects the reported frustration of attempting to predict disease etiology from isolated clinical parameters.[9,13] While this observation is in accord with the reportedly limited spectrum of possible clinical response of the immature brain of young children to inflammation,[13] the significantly higher prevalence of convulsion in the GNB category in the present study would suggest its potential discriminative value in ranking the etiological options in the 2 months–5 years age category. This is a potentially useful tool for the clinician working with limited microbiologic support. Whereas the relatively nonspecific seizure response constitutes a common presentation of intracranial inflammatory lesions in children,[9] the more florid inflammatory response associated with GNB/*H. influenzae* endotoxaemia[14,15] may account for the age-related propensity of GNB meningitis for convulsion in the present study. It may also explain the relatively longer seizure and coma resolution times in this etiological category. The potential clinical import of prolonged seizure as a possible clinical clue of GNB etiology is best appreciated in the young preschool child whose CSF is sterile

Table 4B. Outcome indicators 2: selected investigative parameters according to admission outcome in infants and children with pyogenic meningitis

Parameters	Admission Outcome						Statistical Values χ^2 (P Value)
	Survived	Died	DAMA[1]	Total	Total Assessed	% Mortality	
Gram Smear Categories							
Gram-Smear Neg. (GSN)	12	14	2	28	26	53.9	
Gram-Positive Diplococci	11	9	3	23	20	45.0	
Gram-Negative Bacilli	9	3	2	14	12	25.0	3.30 (0.35)
Gram-Negative Diplococci	1	2	~	3	3	66.7	
Gram-Positive Bacilli	1	~	~	1	1	0	
GSN with TB Meningitis	~	1	1	2	1	100	
CSF Isolates:							
S. Pneumoniae	10	9	3	22	19	47.4	0.35 (0.28)
H. Influenzae	2	~	~	2	2	0	~
N. Meningitidis	~	~	1	1	100	~	
Others¶¶¶	3	~	~	3	3	0	~
CSF Biochem (mg/dl)##							
CSF Protein (mg/dl)							
<150	7 (9)	~ (2)	~ (1)	7 (12)	7 (11)	0 (18.2)	5.79 (0.02)§
≥150	6 (9)	7 (10)	3 (4)	16 (23)	13 (19)	53.9 (52.6)	(2.16 (0.07))
CSF Sugar (mg/dl)							
<1	3 (4)	4 (4)	~ (1)	7 (9)	7 (8)	57.1 (50.0)	3.93 (0.047)§
≥1	5 (7)	~ (3)	2 (3)	7 (13)	5 (10)	0 (33.3)	[0.75 (0.39)]#

‡ Nine children in this category had discharge against medical advice (DAMA) and hence incomplete data; ¶: Attributable to incomplete documentation of CSF parameters; excluded from statistical testing; ¶¶: Gram-positive bacilli and GSN with tuberculous meningitis excluded from analysis; ¶¶¶: Comprises two cases with Klebsiella species isolates, and one each of *S. aureus*, *Acinetobacter* and aerobic spore bearers with Gram-positive bacilli; All excluded from analysis; ##: Represent values for those with positive Gram smears only. Values inclusive of GSN cases are indicated in parentheses in the next row; §: Significant difference(s) shown in the distribution; # Fisher's exact values were 0.07 and 0.35, respectively, for "row <1" and "row >1" mg/dl of CSF sugar

but has the biochemical features of bacterial meningitis. However, in the tropical African setting, the diagnostic reality of cerebral malaria and febrile seizures in the preschool child—both of which are also associated with seizure but requiring different treatment strategies—would probably weigh against predicating etiological prediction on isolated clinical parameters. Besides these other diagnostic possibilities, the morbidity and mortality costs of a belated diagnosis of bacterial meningitis will continue to justify the current local policy of a routine (as against a selective) lumbar puncture (LP) in the preschool child with fever and convulsion, notwithstanding the occasional tragedies.[13] With regard to the putative association of pneumococcal meningitis with anemia, this can be partly ascribed to possible concomitant (but undiagnosed) malaria in this predominant etiologic category, especially as a diagnosis of coexisting malaria was not sought in the present study. Underdiagnosis of pre-existing sickle cell anemia (which poses a significant morbidity burden in West Africa) may also be contributory. While the vulnerability of sickle cell patients to invasive pneumococcal lesions is well known,[9,10] only two cases in this study had confirmatory (hemoglobin) genotype results. Both cases had a fatal outcome, with *S. pneumoniae* isolated from the CSF of the only smear-positive case. Also, the reported importance of concomitant respiratory morbidities in meningococcal disease[16] is in accord with the presence of respiratory symptoms in the two GNC-positive cases.

The identification of GPD/*S. pneumoniae* as the major etiologic category of bacterial meningitis in the current study corroborates the observations in some earlier regional series.[4,8,17,18] Against the background of the well-known association with concomitant pneumococcal pneumonia, this observation is at variance with the reported local rarity of *S. pneumoniae*-associated pneumonia[19,20] and indeed with the reported 11% prevalence of pneumococcal meningitis in Zaria.[21] The high burden of *S. pneumoniae* meningitis identified in the present study may be partly attributed to the local subsistence of several risk factors of invasive pneumococcal disease, especially (urban) overcrowding and poor ventilation.[9,10] These factors are known to favor the premorbid nasopharyngeal acquisition/carriage of the pathogen. A related observation is the inference of a continuing therapeutic efficacy of the current empirical recommendations of penicillin G/ampicillin and chloramphenicol. This is based on the present finding of a high level of pneumococcal sensitivity to penicillin G, ampicillin and chloramphenicol, as well as the uniform sensitivity of the two *H. influenzae* cases to ampicillin and chloramphenicol. Much as cost considerations would favor their continuing relevance in our locale, the modest sample size of positive isolates, as well as the retrospective nature of the present study, would preclude a firm recommendation. Indeed, the clustering of the few resistant isolates towards the end of the present review, as well as contemporary experience of frequent therapeutic failures with penicillin G/ampicillin and chloramphenicol, appears consistent with the observations in recent laboratory-based data from the same hospital,[22] suggesting a significant local level of pneumococcal resistance to penicillin G and ampicillin. This local trend of a rising level of penicillin G/multidrug-resistant pneumococcus

Table 5. Duration of hospital admission in survivors and fatal cases of pyogenic meningitis according to Gram-smear categories

	Gram-Smear Categories						P Value[1]
	GSN	GSP	GPD	GNB	GND	Others (GPB)	GSN vs. GSP (GPC vs. GNB/ vs. GNC)
Survivors							
Mean; SD	12.64; 4.84	16.67; 8.10	16.45; 5.11	16.44;11.36	21	~	0.14 (0.96)
(Variance; n)	(23.45; 11)	(65.63; 21)	(26.1; 11)	(129.03; 9)	(~; 1)	~	
# of Days:							
≤16	9	14	8	6	0	~	0.38 (0.57)
>16	2	7	3	3	1	~	
DAMA	4	5	2	2		1	
Deaths							
Mean; SD	4.99; 8.33	2.8; 2.2	3.72; 2.31	1.67; 0.58	0.63;~	~	0.37 (0.11)
(Variance; n)	(69.35; 12)	(4.96; 14)	(5.32; 9)	(0.33; 3)	(~; 2)	(~; ~)	
# of Days							
≤2	6	7	2	3	2	~	0.69 (0.045)§
>2	6	7	7	0	0	~	
Unknown #	2	2	2	~	~	~	

Statistical testing with one of ANOVA, Yates' or Mantel-Haenszel corrected Chi-squared or Fisher's exact test as appropriate; DAMA: discharge against medical advice; Comprised nine cases with whom the parents either absconded or insisted on leaving despite medical advice to the contrary; §: Significant difference found for the cells compared; #: Attributable to incomplete documentation; Excluded from statistical analyses and *H. influenzae* is consistent with recent reports from the West African subregion.[23-25] Clearly, this emerging trend underscores the need for periodic auditing of local/regional microbiologic data as a prerequisite for formulating effective local/regional treatment policies in pediatric meningitides. Nevertheless, the uniform sensitivity of *S. pneumoniae* and *H. influenzae* to ceftriaxone in the present study, vis à vis the well-known negative "legacies" of a belated or wrong choice of antimicrobials, would appear to justify the prevailing local practice of empirical ceftriaxone for children with GPC- or GNB-positive smears. This is in accord with recent regional recommendations.[22,23,25] With regard to *N. meningitidis*, the paucity of meningococcal meningitis in this study (in the "meningococcal belt" city of Ilorin) underscores the reality of temporal changes in microbiologic data,[9,10,26] even within the same national boundaries. Ongoing antimeningococcal immunization (after the epidemic of 1996) may be contributory to this finding. This and the proven efficacy of the *H. influenzae* type B-conjugate vaccine[10,26-28] are sufficient justifications for incorporating the relevant vaccines (against *S. pneumoniae* and *H. influenzae*) into our present national immunization program. A similar efficacy has recently been shown for the heptavalent CRM_{197} protein-conjugated pneumococcal polysaccharide vaccine.[29,30] Unlike the earlier 23-valent pneumococcal polysaccharide vaccine, the protein-conjugated heptavalent form has the additional advantages of provoking protective responses in children aged <2 years and in causing a significant reduction in (premorbid) nasopharyngeal carriage of the relevant serotypes.[29,30] For the high-risk pediatric population with sickle cell anemia (the morbidity burden of which remains inevitably high in the West African subregion), selective penicillin chemoprophylaxis appears an attractive preventive strategy.[26,29] However, recent reports[22,23,25] of penicillin-resistant pneumococcus in some urban West African communities would hardly justify its endorsement, even for the select pediatric population with sickle cell anemia. Also, the reportedly low isolation rate of *S. pneumoniae* (as against a much higher rate of *S. aureus*) identified recently in bacteremic African children with sickle cell anemia[31] is hardly in favor of its current value in our locale. The preponderance of *S. pneumoniae* [rather than group-B Streptococcus (GBS)] as the major Gram-positive agent in the subset with neonatal meningitis in the present study is interesting for its similarity with earlier Nigerian reports[32-35] and for being at variance with earlier observations in Europe and North America.[10,13,36] That the current rarity of GBS sepsis/meningitis requires further clarification with subsequent studies is underscored by the earlier report of a significant level of GBS maternal vaginal colonization in Nigerian mothers.[37]

In the present study, the poor (short-term) prognostic import of an irregular respiratory rhythm at admission may be explained by a supposedly higher intracranial pressure (and the resultant intracranial anatomic shifts/brain stem compression) in children with this clinical manifestation. Similarly, the association of the two biochemical correlates of meningeal inflammation (i.e., high CSF protein and low CSF sugar) with a fatal outcome may be related to the intense pathogen-associated metabolic activities causing hypoglycorrhacia.[13] The validity of this conventional cause of low CSF sugar, was however, contested in a recent report[38] which attributed hypoglycorrhacia to an increase in the glucose needs of the brain and a consequent switch from aerobic to anaerobic metabolism. The high overall mortality in this study in which pneumococcal meningitis was the predominant etiologic category is consistent with its well-known propensity for a fatal outcome.[8,10,13,23] This is partly attributable to a platelet activating factor (PAF)-simulating component of the pneumococcal cell wall with a propensity for causing increase in the permeability of the "blood-brain barrier" and a resultant profound cerebral edema.[14,38,39] Similarly, the high prevalence of neurological morbidities associated with pneumococcal meningitis in the present study is conceivably related to the severe cerebral edema of the acute phase.[38]

Whereas some earlier reports[12,40] have questioned the justification for fluid restriction in bacterial meningitis, the normal mean serum sodium values across the etiological divide in the present study suggest its continuing local validity for forestalling a possible syndrome of inappropriate antidiuretic hormone (ADH) secretion. Also, for the GNB-positive/*H. influenzae* cases, their propensity for a fatal outcome within a significantly short duration of admission in the present study would buttress the need for streamlining local policies on adjunctive therapy. This is in accord with recommendations on the use of the anti-inflammatory dexamethasone, for mitigating the profligate cytokine response in Gram-negative bacterial meningitides, especially that associated with *H. influenzae* type B.[41,42]

ACKNOWLEDGEMENTS

We recognize with thanks the cooperation at the stage of data collection, of the Records and Microbiology departments of UITH. We also acknowledge with thanks the useful contributions of Drs. John Ojo and Gbenga Mokuolu of UITH. Finally, the corresponding author acknowledges with gratitude the time spared for perusing the initial manuscript by Professor J.C. Azubuike of the Department of Pediatrics, University of Nigeria, Enugu campus, as well as Drs. J.K. Renner and Adegoke Falade of the Colleges of Medicine, University of Lagos and Ibadan, respectively.

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